REMARKS

Applicants have amended the claims to more particularly define the invention taking into consideration the outstanding Official Action. Claims 1 and 20 have been amended to specify that the antibodies or antibody fragments are **polyclonal** and are immobilized by binding or coupling to nanoparticles as clearly supported by Applicants' specification and the discussion therein concerning polyclonal anti-calprotectin antibodies. See for example page 9 first full paragraph and page 15 wherein it is pointed out that calprotectin has numerous antibody binding sites. The objected to expression, "in the range", has been deleted from claims 14 and 15 thereby obviating this aspect of the rejection and claim 26 has been cancelled without prejudiced or disclaimer. Applicants most respectfully submit that all of the claims now present in the application are in full compliance with 35 U.S.C. 112 and are clearly patentable over the references of record.

The Examiner's comments with respect to claim 26 as being directed to a non-elected invention has been considered and this claim has been cancelled while reserving the right to pursue this subject matter in a divisional application.

The Examiner's comments with respect to claim 27 are very much appreciated by the undersigned attorney as well as the further prosecution of the application without issuance of a Notice of Non Complaint Amendment which expedites the prosecution of the application. Again, the Examiner is thanked for the Examiner's courtesy in this regard and in not issuing a Notice of Non Complaint Amendment.

The rejection of claims 14-19, 26 and 28 under 35 U.S.C. 112, second paragraph, as being indefinite has been carefully considered but is most respectfully traversed in view of the amendments to the claims as discussed above. Applicants have cancelled the phrase "in the range" from claim 14 and 15 and it is believed that this amendment obviates this rejection under 35 U.S.C. 112, second paragraph.

Accordingly, it is most respectfully requested that this rejection be withdrawn.

The rejection of claims 14-19 and 28 under 35 U.S.C. 103 (a) as being unpatentable over Arvesen et al in view of Craig et al or in the alternative, as being unpatentable over Craig et al in view of Arvesen et al has been carefully considered but is most respectfully traversed in view of the amendments to the claims and the following comments. It is noted that Arvesen et al does not provide any discussion of the assay method used for making a determination of the marker.

The Craig et al reference relates to covalently bonded high refractive index particle reagents and their use in light scattering immunoassays. As stated in the abstract, novel particle reagents for light scattering immunoassays are provided. The particle reagents are high refractive index shell-core polymers covalently bonded to compounds of biological interest or analogs thereof. A method of measuring unknown concentrations of these compounds of biological interest by measuring changes in turbidity caused by particle agglutination or its inhibition is also provided. There is no specific suggestion or teaching of an assay method for the determination of calprotectin in a calprotectin containing body fluid in accordance with the presently claimed invention.

Applicants have carefully considered the rejection of all the claims on the basis of obviousness over Arvesen in view of Craig. The Official Action states that Craig teaches particle-based immunoassay methods using turbidimetry to detect an analyte. The Official Action also notes that Craig discloses particles having antibodies to an analyte attached thereto.

Applicants wish to stress the importance of how the method of Craig functions in order to understand what is disclosed to the skilled worker by this document. The document must not be considered in light of Applicants' disclosure which is not prior art. Specifically and as would be appreciated by one skilled in the art, the method taught by Craig uses antibody coated particles and employs a polyhapten, which competes with the analyte in solution; higher levels of analyte reduce the binding to the polyhapten and thus reduces the agglutination. Because a poly-hapten is used by Craig, all of the

antibodies must bind to the same epitope of the analyte. If they did not then there could be no competition between the solution analyte and the polyhapten; those recognizing the analyte but not the polyhapten would simply reduce the sensitivity of the assay. Consequently, the method of Craig could not function with multi-site binders such as a polyclonal antibodies as presently claimed.

Since the method of Craig recognizes only one binding site on the analyte, only one antibody can bind per molecule of analyte. This limits the sensitivity of the method.

In contrast to Craig, the present method advantageously employs polyclonal antibodies, as now recited in claim 14, and based upon Example 1 of the application. Because the polyclonal antibodies recognize a variety of sites on the analyte (calprotectin in this case), there is no need for a polyhapten, but rather the agglutination is caused by several particles binding to the same molecule of analyte. Furthermore, since more than two sites exist, more than two particles can potentially be brought together by a single molecule of analyte. This improves the sensitivity in several ways:

1.) The assay produces a positive result – an increase in turbidimetry with increasing concentration rather than a decrease. This makes assessment of low concentrations much more accurate. It is well known in all sciences that the subtraction of two large, error-prone numbers to generate a small result is highly prone to large errors.

2.) A higher concentration of antibody can be used – the method of Craig is a competitive one, meaning that the amount of binder must be limited or the presence of the analyte would have no effect. In excess binder, the analyte would bind but there would still be enough free binding sites to give maximum agglutination. In the present method, more binding sites simply means that more sites on each calprotectin become bound and thus the analyte is more completely utilized.

3.) As indicated above, multi-site binding allows one molecule of analyte to agglutinate more than two particles.

The concentration of calprotectin is extremely low in the fluids analyzed and it is highly unlikely that the method of Craig could be adapted to function with calprotectin. In any case, however, the method of the present invention greatly provides more sensitivity and reliability as a result of using multiple binding sites as opposed to the single site employed in Craig. This is necessary due to the polyhapten format of Craig and the method of Craig cannot be adapted to use polyclonal binders.

The disclosure of Arvesen cannot provide teaching the use of polyclonal antibodies in an agglutination assay because such is not considered in this document.

In view of the above, it is clear that nothing in the combination of Craig with Arvesen could provide for a particle-based agglutination assay for calprotectin utilizing polyclonal antibodies as now claimed. In fact for the reasons discussed above, one of ordinary skill in the art would appreciate that Craig teaches away from the presently claimed invention. The presently claimed invention results in higher sensitivity in a way that is not indicated in any of the prior art. As a result, the present claims cannot be obvious over any combination of Craig with Arvesen. Accordingly, it is most respectfully requested that this rejection be withdrawn.

In section 18, the Official Action rejects the previous submission on the basis that there is nothing in the claims to distinguish the present method form that of Craig. In addition to the inherent unsuitability of the Craig method, the claims are now distinguished by the use of the polyclonal antibodies, which could not function in the Craig method. Accordingly, it is most respectfully requested that this aspect of the rejection be withdrawn.

It is believed that this amendment places the application in condition for allowance but if the Examiner remains of the opinion that the claims are not allowable or there is no indication of allowable subject, an interview is requested with the Examiner to further discuss the application and what if any further amendments or possible evidence could be submitted to establish the patentability of the claimed subject matter. The Examiner is invited to telephone the undersigned attorney in this regard.

In view of the above comments and further amendments to the claims, favorable

reconsideration and allowance of all the claims now present in the application are most respectfully requested.

Respectfully submitted,

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A02_2009.04.22.wpd
January 6, 2010